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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,235	12/19/2005	Alex Cimpoia	SHIRE-518	5723

23599 7590 12/30/2009

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EXAMINER	
ARIANI, KADE	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
12/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/535,235	CIMPOIA ET AL.	
	Examiner	Art Unit	
	Kade Ariani	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on September 16, 2009, has been received and entered.

Claims 1-24 are pending in this application and were examined on their merits.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/16/2009 has been entered.

Applicant's arguments with respect to claims 1-24 have been considered but are moot in view of the new ground(s) of rejection.

Claim Objection

Claim 12 is objected to because of the following informalities:

In claim 12 (line 9) insert –an-- before "enzyme'.

Appropriate correction is required.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cimpoia et al. (WO 00/47759) in view of Janes et al. (in IDS, J. Org. Chem., 1999, Vol. 64, p.9019-9029) and Ferrero et al. (Monatshefte für Chemie, 2000, Vol. 131, p.585-616), and further in view of Adler et al. (JBC, 1961, Vol. 236, No.12, p.3240-3245), is withdrawn.

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janes et al. (in IDS, J. Org. Chem., 1999, Vol. 64, p.9019-9029) in view of Cimpoia et al. (WO 00/47759) and further in view of Ferrero et al. (Monatshefte für Chemie, 2000, Vol. 131, p.585-616) and Martinelle et al. (Biochimica et Biophysica Acta, 1995, Vol. 1258 p.272-276).

Claims 1-11 are drawn to a process for producing a compound of formula I comprising the steps of a) subjecting a compound of formula II to an enzymatic resolution in the presence of an amount of pig liver esterase (or porcine pancreatic lipase), b) recovering compound of formula I, wherein R_1 is a C_{1-12} alkyl, wherein R_2 is a CO-C_{1-6} alkyl, wherein R_2 is a CO-C_{6-12} aryl, the enzyme is pig liver esterase, the

enzyme is porcine pancreatic lipase, replacing the functional group at position C4 of the compound of formula I to produce a compound of formula V, removing the R_2 group, recovering a compound of formula VI, wherein B is purine (or pyrimidine) base, wherein R_3, R_4 ,R_5 , R_6, R_7, and R_8 are H, and further recovering a compound of formula VII, wherein R_1 is methyl and R_2 is benzoyl.

Claims 12-24 are drawn to a process for producing a compound of formula III comprising the steps of, subjecting a compound of formula IV to an enzymatic resolution in the presence of a suitable amount of an enzyme, recovering compound of formula III, wherein R_{11} is $C_{1\text{-}12}$ alkyl, wherein R_{12} is a CO-$C_{1\text{-}6}$ alkyl, wherein R_{12} is a CO-$C_{6\text{-}12}$ aryl, and wherein the enzyme is *Candida Antarctica* lipase A, wherein the enzyme is *C. Antarctica* lipase B, wherein the enzyme is *C. Lypolitica* lipase, wherein the enzyme is *R. Miehei* lipase, replacing the functional group at position C4 of the compound of formula III to produce a compound of formula VIII, removing the R_{12} group, recovering a compound of formula IX, wherein B is purine (or pyrimidine) base, wherein R_3, R_4 ,R_5 , R_6, R_7, and R_8 are H, and further recovering a compound of formula X, and wherein R_{11} is methyl and R_{12} is benzoyl.

Janes et al. teach a process comprising subjecting a compound of formula II (or a compound of formula IV) (2-(*R,S*)-benzoylmethyl-4-(S)-carboxylic Acid 1, 3, Dioxalane Methylester) to an enzymatic resolution in the presence of an amount of an enzyme (a hydrolase), the enzyme is pig liver esterase, wherein R_1 is methyl and R_2 is benzoyl (R_{11} is methyl and R_{12} is benzoyl) (p.9021 2nd column 1st paragraph Figure 2. in "trans-2" compound Bn = benzoyl & Me = methyl, and p.9022 Table 1., 1st column "esterases"

row 36). It must be noted that methyl has formula CH3- and therefore is a C_{1-12} alkyl, and benzoyl has formula $CO-C_6H_5$ - therefore is a $CO-C_{1-6}$ aryl and/or $CO-C_{6-12}$ aryl. Janes et al. also teach using *Candida Antarctica* lipase A , *C. Lypolitica* lipase, *Miehei* lipase, *C. Lypolitica* esterase (p.9022 Table 1. "lipases. Row 3, 4 10 and "esterases" row 6). Janes et al. further teach pig liver esterase is being used to enantioselectively hydrolyze butyryl esters of FTC (a nucleoside analogue) (p.9020 3rd paragraph lines 4-5).

Janes et al. do not teach recovering compound of formula II (formula III), replacing the functional group at position C4 of the compound of formula I (formula III) to produce a compound of formula V (formula VIII), removing the R_2 group of the compound of formula V (formula VIII), recovering the compound of formula VI (formula IX), wherein B is a purine (or pyrimidine) base, wherein R_3, R_4 ,R_5 , R_6, R_7, and R_8 are H, the enzyme is porcine pancreatic lipase, and wherein the enzyme is *C. Antarctica* lipase B. However, Cimpoia et al. teach a process of making dioxalane nucleoside analogs with a high degree of steric purity which includes the use of certain hydrolytic enzymes (p.7 2nd paragraph). Cimpoia et al. teach the process further comprising replacing the functional group at position C4 of the compound, removing the R_2 group (R_{12} group), recovering a compound of (formula VI, formula IX) wherein B is purine (or pyrimidine) base, wherein R_3, R_4 ,R_5 , R_6, R_7, and R_8 are H, and further recovering the compound of (formula VII , formula X) (Abstract, page 7 2nd-4th paragraphs, page 8 2nd paragraph, page 11 2nd and 3rd paragraphs). Cimpoia et al. further teach modifications and

variations of the present invention including but not limited to selection of enzymes and optimization of reaction conditions will be obvious (page 68 last paragraph).

Ferrero et al. teach enzyme-catalyzed reactions have become standard procedures for the synthesis of enantiomerically pure compounds for their simple feasibility and high efficiency, the enzymes commonly used including pig liver esterase, porcine pancreas lipase, and C. *Antarctica* lipase CAL also called CAL-B (p.586 Table.1. first column lines 2, 5 and 6). Ferrero et al. also teach CAL (C. *Antarctica* lipase B) showed higher regioselectivity toward primary hydroxyl group of both deoxy- and ribonucleotides (p.597 4th paragraph lines 7-8). Ferrero et al. further teach using lipase from porcine pancreas (PPL) as a catalyst to selectively attack 5'-O-acetyl group I with very good yield (p.593 2nd paragraph lines 2-4).Therefore, a person of ordinary skill in the art would at the time the invention was made would have recognized that the choice of the enzyme to be used in the process of making nucleoside analogs would have depended on the regioselectivity and substrate specificity of the enzyme and the type of the compound/analogue that is being produced.

Martinelle et al. teach catalytic behavior C. *Antarctica* lipase B (CALB) was more typical of an esterase than a lipase (p.275 2nd column 4th paragraph lines 1 and 4-5). Therefore, a person of ordinary skill in the art would have been motivated to use this enzyme for diastereomeric resolution of a methylester, due to its esterase behavior.

Therefore, in view of the above teachings, a person of ordinary skill in the art at the time the invention was made, would have been motivated to combine the teachings of Cimpoia et al. and Janes et al. in order to provide a method for producing a

compound (formula I or III), e.g. a dioxalane nucleoside analogue, with a reasonable expectation of success in producing the compound, because Janes et al. teach pig liver esterase used to enantioselectively hydrolyze butyryl esters of a nucleoside analogue.

Moreover, a person of ordinary skill in the art at the time the invention was made, recognizing that the choice of the enzyme to be used in the process would have depended on the regioselectivity and substrate specificity of the enzyme and type of the compound being produced, would have been motivated to try and to use porcine pancreatic lipase and *C. Antarctica* lipase B (from finite number of identified enzymes) as taught by Ferrero et al. to provide a process for producing a compound with formula I (a dioxolane nucleoside analogue) with a reasonable expectation of success, because Ferrero et al. teach C. *Antarctica* lipase B showed higher regioselectivity toward primary hydroxyl group of both deoxy- and ribonucleotides, and selectively of porcine pancreas lipase as a catalyst to attack 5'-O-acetyl group with very good yield.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on IFP.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kade Ariani/
Examiner, Art Unit 1651